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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/544,910	04/07/2000	Yadong Huang	06510/121US1	2429

24353 7590 05/23/2006

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/544,910	HUANG ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8 and 11-35* is/are pending in the application.

4a) Of the above claim(s) *12-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 15, 2005 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed on August 1, 2005 has been considered. Rejections and/or objections not reiterated from the previous office action mailed April 5, 2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Election

Applicant's election with traverse of claims 1, 4-8, and 11 (reciting an antisense nucleic acid) in the reply filed on April 20, 2006 is acknowledged. The traversal is on the ground(s) that there is no unduly burdensome search on all claims of the instant application. This is not found persuasive because the methods of groups I-III would require different key word searches due to

their materially different subject matter recognized in the art, which would pose a search burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-8 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 4-8 and 11 are drawn to a method of reducing the plasma level of VLDL in a host by administering antisense against apoE3 (claim 4) or a method of treating a host suffering from hyperlipidemia Type IV (claim 7) or Type IIb (claim 8), comprising administering to said host an effective amount of an antisense nucleic acid, wherein said antisense nucleic acid reduces the plasma amount of active apoE by reducing the expression of apoE via reducing VLDL production by at least two fold, wherein said apoE is apoE3 (claim 11).

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), and they include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the

prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In view of *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) and *In re Cortright* 165 F.3d 1353,1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999), the pending claims must be "given their broadest reasonable interpretation consistent with the specification."

In light of the above, the instant specification defines the scope of the method of treating a host by the treatment which entails "at least an amelioration of the symptoms associated with the pathological condition afflicting the host, where amelioration is used in a broad sense to refer to at least a reduction in the magnitude of a parameter, *e.g.*, symptom, associated with the pathological condition being treated, such as elevated plasma VLDL or triglyceride levels....As such, treatment also includes situations where the pathological condition, or at least symptoms associated therewith, are completely inhibited, e.g. prevented from happening, or stopped, *e.g.* terminated..." (page 20).

With regard to amelioration of pathological symptoms associated with hyperlipidemia, the instant specification has not shown any *in vivo* working examples wherein subjects suffering from hyperlipidemia present reduced severity of symptoms (i.e., elevated VLDL levels are reduced) or the symptoms are completely inhibited after the administration of the antisense oligonucleotide targeting apoE3. The entire instant specification discloses examples pertaining to transgenic animal models having lipid profiles analogous to those observed in human

hyperlipidemic subjects, in which overexpression of apoE3 correlates with increased VLDL levels (pages 20-42). In other words, the instant specification is silent with respect to whether or not an antisense targeting apoE3 correlates with amelioration or prevention of hyperlipidemic symptoms, since there is no single representative *in vivo* example demonstrating the ameliorative or preventive effects of the apoE3 antisense oligonucleotide in reducing VLDL levels in a host suffering from elevated plasma levels of VLDL or hyperlipidemia. In fact, an antisense oligonucleotide sequence targeted against apoE3 is not even disclosed in the instant application.

Antisense approaches to gene therapy have been proposed about two decades ago (see Zon, *Pharmaceutical Research,* 5:539-549, 1988), and clinical applications of antisense approaches began to surface with five clinical trials of antisense pharmaceutical drugs (see Mercola et al., *Cancer Gene Therapy,* 2:47-59, 1995). Nevertheless, Mercola et al., add cautionary remarks concerning the prospects of the antisense gene therapy as following:

> "But, in practice, as with any therapeutic modality, problems arise, notably; (a) degradation of the oligomer...;(b) inefficient cell uptake; (c) nonspecific binding; (d) nonspecific cleavage of mRNA." (page 49)
>
> "The therapeutic application of oligonucleotides and their derivatives is very much in its infancy....It is to be hoped that human diseases of genetic origin will eventually yield to approaches based on these genetic medicines." (page 50)

In addition, Mercola et al., further note that a phase I clinical trial employing graded doses of an antisense p53 oligonucleotide has failed to show therapeutic effects *in vivo*. In support of this, a more recent prior art published close to the effective filing date of the instant application (April 12, 1999) by Branch (*TIBS,* 23:45-50, February 1998) also notes the importance of the time and expense necessary to screen large numbers of potential antisense molecules and to carefully monitor their *in vivo* effects, due to non-antisense effects and limits of specificity as well as accessibility of the antisense molecules. In light of the prior art teachings of both Mercola et al.,

and Branch, the total lack of the *in vivo* apoE3 antisense oligonucleotide examples, let alone the absence of even a single antisense sequence in the instant disclosure, would necessitate undue experimentation in order for a skilled artisan to practice the claimed invention. Clearly, enablement of the instantly claimed invention cannot be predicted on the basis of the factors listed above on page 3 herein.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Dana Shin
Examiner
Art Unit 1635

D. Shin

5-17-2006

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER